REMARKS

The Official Action dated April 10, 2002 has been carefully considered. Accordingly, the changes presented herewith, taken with the following remarks, are believed sufficient to place the present application in condition for allowance. Reconsideration is respectfully requested.

By the present Amendment, the specification is amended to include disclosure from SE 9704935-7, page 2, lines 1-8, which is incorporated by reference at page 18 of the present application. A certified translation of SE 9704935-7 is enclosed.

Additionally, claim 1 is amended to include limitations from previous claims 5 and 7 and from the specification at page 8, line 6, page 9, lines 8-32 and page 10, lines 1-5. Claim 20 is amended to include a limitation from page 23, lines 27-30. Claims 1 and 20 and claims 6, 11-17, 21 and 24 are also amended for various matters of form and clarity. A Version With Markings Showing Changes Made is attached. It is believed that these changes do not involve any introduction of new matter, whereby entry is believed to be in order and is respectfully requested.

In accordance with the Examiner's request, an Abstract on a separate sheet is provided herein.

Claims 1-31 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite. This rejection is traversed with respect to present claims 1-4, 6 and 11-31, as it is believed that the present claims particularly point out and distinctly claim the subject matter which Applicants regard as the invention in accordance with the requirements of 35 U.S.C. §112, second paragraph. Reconsideration is respectfully requested.

More specifically, the Examiner had indicated various informalities in the claims which Applicants believe that the amendments presented herewith overcome. The Examiner had also asserted that the terms Reactant I, Analyte', Reactant*, upstream, Capturer, firmly

and equivalent binding sites are vague and/or indefinite. Applicants submit however that each of these terms is sufficiently defined in the specification to render use of the terms definite to one of ordinary skill in the art. For example, at page 1, beginning at line 25 and in claim 1, Analyte' is defined as an analyte in a sample or an analyte-related reactant, i.e., an added biospecific affinity reactant included in the complex in an amount which is related to the amount of analyte in the sample. The specification at page 1, beginning at line 11, and claim 1 also define Reactant I and Reactant* as reactants exhibiting biospecific affinity to the analyte, with Reactant* further being defined as analytically detectable. Claim 20 similarly defines Reactant* as an analytically detectable reactant. Reactants exhibiting biospecific affinity are described in detail at, for example, page 2, lines 10-18. Thus, these terms are definite to one of ordinary skill in the art in view of the present specification and claims.

With respect to the term "upstream," this term is used to further describe a flow matrix and a process flow stream. Applicants submit that this term is well known in the art, as described in any dictionary as indicating a preceding relative position in a flow stream. Upstream and downstream are used in the present claims in their regular and ordinary use and no further clarification is believed to be required.

Capturer is defined in the specification, beginning at page 2, line 3, as a reactant which is firmly anchored to the matrix in the detection zone and may be Reactant I or a reactant which has biospecific affinity to Reactant I or to another reactant which in turn, optionally via one or more additional reactants, has biospecific affinity to Reactant I. Thus, Capturer is defined in the present specification and the use of this term in the claims is definite to one of ordinary skill in the art.

With respect to the term "firmly," the Examiner's attention is directed to the specification at page 2, lines 3-8, page 12, lines 20-32, page 13, lines 5-14 and page 14, lines 15-17. From these passages and the remaining teachings of the specification, one of ordinary

skill in the art will recognize that the term "firmly anchored" indicates that the Capturer is immobilized on the matrix under conditions which do not allow release during the subject flow determination. Thus, the term "firmly anchored" is definite to one of ordinary skill in the art.

With respect to the phrase "equivalent binding sites," the Examiner's attention is particularly directed to the specification at page 2, line 30 - page 3, line 3 which clearly defines the phrase "equivalent binding sites." Thus, this phrase is definite to one of ordinary skill in the art.

It is therefore submitted that claims 1-4, 6 and 11-31 are definite in accordance with the requirements of 35 U.S.C. §112, second paragraph, whereby the rejection has been overcome. Reconsideration is respectfully requested.

Claims 1-5, 7, 17 and 18 were rejected under 35 U.S.C. §102(b) as being anticipated by the Robinson et al published PCT application WO 95/16914. The Examiner asserted that Robinson et al disclose a method and device for determining an analyte in a sample involving biospecific affinity reactions with the use of calibration zones in which a calibration reagent is immobilized and has biospecific affinity for the analyte of interest or a binding partner of interest. The Examiner also asserted that Robinson et al disclose that the specific binding partner can be coupled to or conjugated to the calibrator to form a complex for detection, the device may be a flow-through device, and multiple measurement zones may be employed.

However, Applicants submit that the methods defined by claims 1-4, 17 and 18 are not anticipated by Robinson et al and are patentably distinguishable therefrom. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

As defined by claim 1, the present invention is directed to a lateral flow method for the determination of an analyte in a sample involving utilizing biospecific affinity reactions. The method comprises forming a complex comprising Reactant I --- Analyte' --- Reactant*

wherein Reactant* and Reactant I exhibit biospecific affinity to the analyte, Reactant* is analytically detectable, and Analyte' is the analyte or an analyte-related reactant. The method further comprises determining a detectable signal from Reactant* in the complex (sample value), and obtaining the amount of analyte in the sample by comparing the sample value with one or more calibrator values, each of which corresponds to a standard amount of analyte. Before determination of the calibrator value, either calibrator or a binder for the calibrator has been bound to a matrix and the calibrator is added or calibrator predeposited in the matrix is released at the determination of calibrator value. The matrix is insoluble in the liquid medium in which binding of Reactant* to the calibrator occurs. The calibrator and the analyte have the ability to biospecifically bind to Reactant* via equivalent binding sites, and one or more calibrator zones comprising calibrator or binder for the calibrator are located in the same process flow as Reactant I in a detection zone.

The methods according to the present invention provide improvements in analyte determinations employing calibrators. Particularly, the present methods enable compensation for the differences that may exist between calibrator and sample solution and between runs performed at different times and/or different places. These advantages are obtained by the defined methods of claim 1, employing Reactant* wherein the calibrator zone or zones are located in the same process flow as the detection zone for measuring analyte.

Robinson et al disclose a sensor device for sandwich assay which comprises a measurement zone and a reference zone. The measurement zone includes an immobilized first specific binding partner for the ligand under assay and a first amount of an optionally labeled second specific binding partner for the ligand under assay. The reference zone includes an immobilized first specific binding partner for the ligand under assay, a second known amount of an optionally labeled second specific binding partner for the ligand under assay and a known amount of ligand analog. The second known amount of the second

specific binding partner is less than the first amount. Use of the Robinson et al device is described beginning at page 10, line 1. One skilled in the art will appreciate that a portion of sample is applied to the measurement zone of the sensor device while another portion of sample is applied to the reference zone of the sensor device. The reference zone is used to alert the user that the concentration of analyte present in the sample is greater than a high-dose hook concentration whereby the user can then dilute a sample for further measurement.

Thus, the sensor device of Robinson et al provides the reference zone in a flow stream separate from the measurement zone. Applicants find no teaching or suggestion by Robinson et al of a lateral flow method as defined by claim 1 wherein a calibrator and an analyte have the ability to biospefically bind to an analytically detectable reactant (Reactant*) via equivalent binding sites and wherein a calibrator zone comprising calibrator or binder is located in the same process flow as Reactant I in a detection zone. Additionally, Applicants find no teaching or suggestion by Robinson et al relating to the advantages provided by the presently claimed methods, wherein the calibration is relevant to a particular sample and the conditions under which the sample is processed through the process flow stream and compensation is enabled for differences between calibrator and sample solution as well as between runs performed at different times and/or at different places.

Anticipation under 35 U.S.C. §102 requires that each and every element as set forth in the claims is found, either expressly or inherently described, in a single prior art reference, *In re Robertson*, 49 U.S.P.Q.2d 1949 (Fed Cir. 1999). In view of the deficiencies in the teachings of Robinson et al, Robinson et al do not anticipate claims 1-4, 17 and 18 under 35 U.S.C. §102. It is therefore submitted that the rejection has been overcome. Reconsideration is respectfully requested.

Claims 6 and 8-16 were rejected under 35 U.S.C. §103(a) as being unpatentable over Robinson et al in view of the Davis et al U.S. Patent No. 6,352,862. Claims 20-25 and 27-31

were also rejected under 35 U.S.C. §103(a) as being unpatentable over Robinson et al in view of Davis et al. The Examiner asserted that Robinson et al fail to teach transporting Reactant* through the calibrator zones but relied on Davis et al as disclosing a lateral flow device incorporating a labeled specific binding reagent which is freely mobile when in the moist state. The Examiner asserted that it would have been obvious to incorporate transportation of a labeled specific binding reagent as taught by Davis et al in the method and device of Robinson et al.

However, Applicants submit that the methods defined by claims 6 and 11-16 and the devices and kits defined by claims 20-25 and 27-31 are nonobvious over and patentably distinguishable from Robinson et al in view of Davis et al. Accordingly, these rejections are traversed and reconsideration is respectfully requested.

The methods of claim 1, on which claims 6 and 11-16 depend, are discussed above. According to claim 20, the present invention is directed to a device for transforming measured signal values of a complexed, analytically detectable reactant (Reactant*) to real amounts of analyte in a sample in connection with performing an analysis method which utilizes biospecific affinity reactions for the determination of the amount of analyte in a sample to form complexes comprising Reactant* in an amount which is related to the amount of analyte in the sample. The device exhibits a flow matrix in which there is an area of process flow for the transport of Reactant*. In the area of process flow, there are one or more calibrator zones comprising a calibrator or binder for the calibrator, which is firmly anchored to the matrix, an application zone for Reactant* upstream of the one or more calibrator zones, and one or more detection zones downstream of the one or more calibrator zones. The amounts of calibrator or calibrator binder, respectively, are different for at least two calibrator zones, and the calibrator exhibits binding sites to which Reactant* binds when Reactant* is

transported through a calibrator zone. Claims 29-31 are directed to test kits comprising such a device.

The deficiencies of Robinson et al with respect to the claimed methods are discussed above. Additionally, Applicants find no teaching or suggestion by Robinson et al of a device as defined in claim 20 wherein one or more calibrator zones are provided, together with an application zone for analytically detectable reactant (Reactant*) upstream of the one or more calibrator zones and one or more detection zones downstream of the one or more calibrator zones. Similarly, Applicants find no teaching or suggestion by Robinson et al relating to the advantages provided by the presently claimed methods and devices wherein compensation is enabled for differences between calibrator and sample as well as between runs performed at different times and/or different places. These deficiencies are not resolved by Davis et al.

More particularly, Davis et al disclose an analytical test device for immunoassays. A labeled reagent is incorporated in a separate macroporous body through which a liquid sample migrates before the sample migrates through a carrier material to a detection zone. In one embodiment, a control zone may be provided downstream of the detection zone and loaded with an antibody that will bind to the labeled reagent to confirm that the sample has permeated the test strip. However, Applicants find no teaching or suggestion by Davis et al for modifying the sensor device of Robinson et al to result in the presently claimed method. Specifically, Applicants find no teaching or suggestion by Davis et al of a lateral flow method wherein a calibrator zone and a detection zone are provided in the same process flow, particularly in the manner required by the method of claim 1 or the device of claim 20. In fact, Applicants find no teaching or suggestion by Davis et al relating to any calibrator zones or the use of calibrator values. Thus, Davis et al do not resolve the deficiencies of Robinson et al.

In order to render a claimed invention obvious, the prior art must enable one skilled in the art to make and use the claimed invention, *Motorola, Inc. v. Interdigital Tech. Corp.*, 43 U.S.P.Q.2d 1481, 1489 (Fed. Cir. 1997). In view of the deficiencies in the teachings of Davis et al, the combination of Robinson et al and Davis et al does not enable one skilled in the art to perform the lateral flow method as recited in claim 1, or claims 6 and 11-16 dependent thereon, or to make and use the devices of claims 20-25, 27 and 28 or the test kits of claims 29-31. Thus, the methods defined by claims 6 and 11-16, the devices defined by claims 20-25, 27 and 28, and the kits defined by claims 29-31 are nonobvious over and patentably distinguishable from the combination of Robinson et al and Davis et al, whereby the rejections under 35 U.S.C. §103 have been overcome. Reconsideration is respectfully requested.

Claim 19 was rejected under 35 U.S.C. §103(a) as being unpatentable over Robinson et al in view of Davis et al and further in view of the Self U.S. Patent No. 4,446,231. The Examiner relied on Self as disclosing that immunoassays are used for detection and/or determination of autoimmune diseases.

However, Applicants submit that the methods defined by claim 19 are nonobvious over and patentably distinguishable from the teachings of Robinson et al, Davis et al and Self. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

The deficiencies of Robinson et al and Davis et al with respect to claim 1, on which claim 19 depends, are discussed in detail above. Self does not resolve these deficiencies. That is, Self discloses an immunoassay employing an enzyme label which converts a precursor into a cycling factor which in turn is interconverted in a cycling detection system. Applicants find no teaching or suggestion by Self relating to a lateral flow method as defined in present claim 1 and employing one or more calibration zones, particularly in the same process flow as a detection zone. Thus, the combination of Robinson et al, Davis et al and

Self does not enable one of ordinary skill in the art to conduct the method of claim 1 and therefore does not render claim 1, or claim 19 dependent thereon, obvious. It is therefore submitted that the rejection of claim 19 under 35 U.S.C. §103 based on Robinson et al, Davis et al and Self has been overcome. Reconsideration is respectfully requested.

Claim 26 was rejected under 35 U.S.C. §103(a) as being unpatentable over Robinson et al in view of Davis et al and further in view of the Weng et al U.S. Patent No. 4,740,468. The Examiner relied on Weng et al as disclosing the use of a specific binding partner that is biospecific to a second binding partner which in turn is specific for an analyte. The Examiner asserted it would have been obvious to incorporate an immobilized specific binding partner as taught by Weng et al in the device of Robinson et al.

However, Applicants submit that the device defined by claim 26 is nonobvious over and patentably distinguishable from the combination of Robinson et al, Davis et al and Weng et al. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

The deficiencies of Robinson et al and Davis et al have been discussed above with respect to claim 20, on which claim 26 depends, and are not resolved by Weng et al. That is, Weng et al disclose a method and device for determining the presence of an analyte in a sample suspected of containing the analyte. Applicants find no teaching or suggestion by Weng et al relating to a test device including a calibration zone, or for modifying the device of Robinson et al to arrive at a device as defined by claim 20 on which claim 26 depends. Thus, Weng et al do not resolve the deficiencies of Robinson et al and Davis et al. It is therefore submitted that the rejection under 35 U.S.C. §103 based on these references has been overcome. Reconsideration is respectfully requested.

Finally, claims 29-31 were rejected under 35 U.S.C. §103(a) as being unpatentable over Robinson et al in view of Davis et al and further in view of the Boguslaski et al U.S. Patent No. 5,420,016. The Examiner relied on Boguslaski et al as disclosing assembling

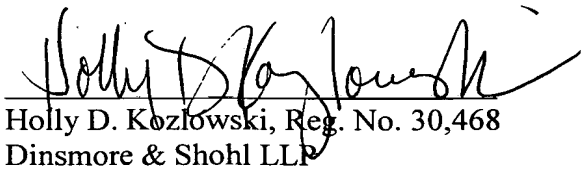
system components into a test kit. The Examiner asserted it would have been obvious to assemble the components into kits such as taught by Boguslaski et al.

However, Applicants submit that the test kits defined by claims 29-31, employing the device of claim 20, are nonobvious over and patentably distinguishable from the combination of Robinson et al, Davis et al and Boguslaski et al. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

More particularly, the test kits of claims 29-31 comprise a device according to claim 20. The deficiencies of Robinson et al and Davis et al with respect to the device of claim 20 are discussed in detail above. These deficiencies are not resolved by Boguslaski et al, and the teachings of Boguslaski et al relating to a kit do not render obvious the test kit defined by claims 29-31. That is, Boguslaski et al disclose a method, device and kit for determining the presence of *Helicobacter pylori* in a biological specimen. Applicants find no teaching or suggestion of a device as recited in claim 20, particularly including one or more calibrator zones. Similarly, Applicants find no teaching or suggestion by Boguslaski et al for modifying any of the teachings of Robinson et al or Davis et al to arrive at the presently claimed test kits employing a device as recited in claim 20. The mere teaching of a test device and kit by Boguslaski et al does not render any feature of the presently claimed test kits obvious. It is therefore submitted that the test kits defined by claims 29-31 are nonobvious over and patentably distinguishable from Robinson et al, Davis et al and Boguslaski et al, whereby the rejection under 35 U.S.C. §103 based on these references has been overcome. Reconsideration is respectfully requested.

It is believed that the above represents a complete response to the rejections under 35 U.S.C. §§ 102, 103 and 112, second paragraph, and places the present application in condition for allowance. Reconsideration and an early allowance are requested.

Respectfully submitted,



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VERSION WITH MARKINGS SHOWING CHANGES MADE

In the Specification:

The paragraph at page 1, lines 32 - page 2, line 8, is amended as follows:

--This type of analytical methods has been carried out [i.a.] in so-called flow matrices, whereby reactants including analyte are transported in a process flow through the matrix (= flow methodology) to a detection zone (DZ) where Reactant* is captured in an amount related to the amount of analyte in the sample. Capture occurs via a reactant (Capturer) which is firmly anchored to the matrix in DZ. That is, the Capturer is bound via bonds which are stable under the conditions used to capture Reactant* in the detection zone. The Capturer may be Reactant I or a reactant which has biospecific affinity to Reactant I or to another reactant, which in turn, optionally via one or more additional reactants, has biospecific affinity to Reactant I.--

In the Claims:

Claims 1, 6, 11-17, 20, 21 and 24 are amended as follows:

1. (Twice Amended) A lateral flow method [in a process] for the determination of an analyte in a sample involving utilizing biospecific affinity reactions, and comprising the following steps:

i. forming a complex comprising:

Reactant I---Analyte'---Reactant*, where

a. Reactant* and Reactant I exhibit biospecific affinity to the analyte,

b. Reactant* is analytically detectable,

c. Analyte' is the analyte or an analyte-related reactant, and subsequently

ii. determining a [the] detectable signal from Reactant* in the complex (sample value), and

iii. obtaining the amount of analyte in the sample by comparing the sample value with one or more calibrator values, each of which corresponds to a standard amount of analyte,

wherein A) before [the] determination of the calibrator value, either (i) [the] calibrator or (ii) a binder for the calibrator has been bound to a matrix, and when a binder for the calibrator has been bound to the matrix, calibrator is added or calibrator predeposited in the matrix is released at the determination of calibrator value, and wherein the matrix is insoluble in the liquid medium in which binding of Reactant* to the calibrator occurs, B) the calibrator and the analyte have the ability to biospecifically bind to Reactant* via equivalent binding sites, and C) one or more calibrator zones CZ comprising calibrator or binder for the calibrator are located in a single process flow stream with Reactant I in a detection zone (DZ).

6. (Twice Amended) The method according to claim 1, wherein

a. [the matrix is a flow matrix exhibiting one or more calibrator zones (CZ1, CZ2, CZ3, etc.),

b.] (i) each calibrator zone comprises calibrator in an amount corresponding to a standard amount of analyte, or

(ii) each calibrator zone contains calibrator binder, the amount of calibrator binder and the amount of calibrator corresponding to a standard amount of analyte, and

b. [c.] Reactant* is bound to the calibrator by transporting Reactant* through the calibrator zones.

11. (Twice Amended) The method according to claim 1, wherein along a single [the] matrix is a flow matrix, and wherein along [one and the same] a single process flow stream, there are

a. one or more calibrator zones (CZ), each of which exhibits a matrix calibrator or a matrix calibrator binder,

b. one or more detection zones (DZ), none of which coincides with any calibrator zone, and in which a Capturer is firmly anchored and is either Reactant I or a biospecific affinity reactant, which directly or indirectly binds [is able to bind] Reactant I biospecifically,

c. an application zone for Reactant*, $A_{R*}Z$, which is located upstream of said CZ and DZ and to which Reactant* is optionally [may have been] predeposited, and

d. an application zone for sample (A_SZ) which is located

i. upstream of or coinciding with a detection zone,

ii. downstream or upstream of or coinciding with $A_{R*}Z$ ($A_SZ/A_{R*}Z$), or

iii. upstream of, downstream of or coinciding with a calibrator zone,

wherein [preferably] the zone of application of sample (A_SZ) is located upstream of both detection and calibrator zones, and wherein [in that] Reactant* is added to $A_{R*}Z$ if Reactant* is not predeposited, or buffer is added to $A_{R*}Z$ if Reactant* is predeposited, and sample is added to A_SZ, optionally premixed with Reactant* if A_SZ and $A_{R*}Z$ coincide, such that analyte and Reactant* reach DZ at the same time, or such that analyte reaches DZ before Reactant*.

12. (Twice Amended) The method according to claim 11, wherein the calibrator zone or zones [(KZ)] CZ exhibit a calibrator binder, and [that] calibrator is predeposited upstream of the calibrator zone or zones.

13. (Twice Amended) The method according to claim 11, wherein the process flow stream comprises two or more of said calibrator zones.

14. (Twice Amended) The method according to claim 11, wherein the process flow stream comprises one or two of said calibrator zones, and [in that] the level of analyte in the sample is obtained by:

a. having access to one or more separately obtained calibrator values, and

b. comparing a calibrator value for a calibrator zone (Positive Internal Calibrator = PIC), [being] located in the [same] process flow [as said] stream including the detection zone, with one or more of the separately obtained calibrator values,

c. adapting the measurement signal from the detection zone to the deviation of the measurement signal for PIC from the separate calibrator values, and subsequently

[d.] obtaining the level of analyte in the sample by comparing the adapted measurement signal from the detection zone with one or more of the separately obtained calibrator values[, or vice versa with respect to what has been adapted and compared in steps c and d].

15. (Twice Amended) The method according to claim 11, wherein

a. A_SZ is (i) common to $A_{R*}Z$, forming a common zone (= $A_SZ/A_{R*}Z$) or (ii) is located upstream of $A_{R*}Z$, and

b. for alternative (i) sample is premixed with Reactant* before it is added to the common zone $A_SZ/A_{R*}Z$, or sample is [being] added to the common zone $A_SZ/A_{R*}Z$ containing predeposited Reactant*, and for alternative (ii), sample is added to A_SZ, which is located upstream of $A_{R*}Z$ which in turn comprises predeposited Reactant*.

16. (Twice Amended) The method according to claim 6, wherein Reactant* has particles as an analytically detectable group, and/or calibrator or calibrator binder [and/or Capturer, if there is a detection zone,] is/are anchored to the matrix [via] by particles.

17. (Twice Amended) The method according to claim 1, wherein the analyte is an antibody directed to Reactant I or to Reactant*, and

a. Reactant* is an antibody directed to the analyte and Reactant I is an antigen [/] or hapten, when the analyte is an antibody directed to Reactant I, or [and]

b. Reactant* is an antigen or a hapten and Reactant I is an antibody directed to the analyte, when the analyte is an antibody directed to Reactant*.

20. (Twice Amended) A device for transforming measured signal values of a complexed, analytically detectable reactant (= Reactant*) to real amounts of analyte in a sample, in connection with performing an analysis method which utilizes biospecific affinity reactions for the determination of the amount of analyte in a sample, to form complexes comprising Reactant* in an amount which is related to the amount of analyte in the sample, wherein the device exhibits:

a flow matrix in which there is an area of process flow for the transport of Reactant*, and wherein there are [is] in said [this] area

i. one or more calibrator zones [(CZ1, CZ2, etc.)] (CZ) comprising a calibrator, or binder for the calibrator, which is firmly anchored to the matrix, the amounts of calibrator or calibrator binder, respectively, being different for at least two calibrator zones when at least two calibrator zones are present, and the calibrator exhibiting binding sites to which Reactant* binds [is able to bind], when Reactant* is transported through a calibrator zone, [and]

ii. an application zone for Reactant* ($A_{R*}Z$) upstream of said one or more calibrator zones, and

iii. one or more detection zones (DZ) downstream of said one or more calibrator zones.

21. (Twice Amended) The device according to claim 20, wherein a calibrator binder is firmly anchored in the matrix and [that] the device comprises calibrator predeposited upstream of the calibrator zone[, for example in A_SZ].

24. (Twice Amended) The device according to claim 23, wherein $A_{R*}Z$ is located upstream of or downstream of or coincides with A_SZ[, where upstream or downstream locations are preferred].

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